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UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte JAMES N. PETITTE and YI GUO ZHANG

Appeal 2007-4488
Application 09/757,054
Technology Center 1600

Decided: February 25, 2008

Before DEMETRA J. MILLS, ERIC GRIMES, and JEFFREY N.
FREDMAN, *Administrative Patent Judges*.

Opinion for the Board filed *per curiam*.

Opinion Concurring filed by *Administrative Patent Judge* FREDMAN.

PER CURIAM.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a culture of undifferentiated chicken cells expressing an embryonic stem cell phenotype, which the Examiner has rejected on grounds of new matter, nonenablement, indefiniteness, anticipation, obviousness, and double patenting. We have jurisdiction under 35 U.S.C. § 6(b). We affirm in part.

BACKGROUND

“Undifferentiated avian cells expressing an ESC [embryonic stem cell] phenotype are useful, among other things, as a tool for the study of embryological development . . . and the production of transgenic poultry” (Spec. 3). The Specification discloses that an embryonic cell phenotype “refers to undifferentiated avian cells having a large nucleus, a prominent nucleolus, and little cytoplasm” (Spec. 9). The Specification states that

embryonic germ cells and embryonic stem cells are phenotypically the same in that they appear to be the same upon microscopic inspection (despite reported differences in methylation of some genes), display the same immunological markers, and are functionally the same in that both have been shown to differentiate extensively in culture and to contribute to chimeras when injected into host blastocysts, thus demonstrating their pluripotent and totipotent nature.

(Spec. 9).

Appellants teach “an object of the present invention was to develop and provide a process that would permit the development of undifferentiated avian cells expressing an embryonic stem cell phenotype from avian PGCs [primordial germ cells]” (Spec. 8).

STATEMENT OF THE CASE

The Claims

Claims 44, 47, 48, 51-54 and 56-58 are on appeal. Claims 44, 47, 48, 53, 54, and 58 were separately argued. The remaining claims have not been argued separately and therefore stand or fall together with the claim from

which they depend. 37 C.F.R. § 41.37(c)(1)(vii). We will focus on claims 44, 47, 48, 53, 54, and 58, which are representative and read as follows:

44. A sustained culture of undifferentiated chicken cells expressing an embryonic stem cell phenotype, the sustained culture comprising:

(a) a preconditioned feeder matrix;

(b) conditioned media;

(c) chicken primordial germ cells and chicken stromal cells, wherein the chicken primordial germ cells and stromal cells are isolated together from the embryonic genital ridge or gonad from a chicken embryo at a stage later than stage 14 according to the Hamburger & Hamilton staging system; and

(d) undifferentiated chicken cells expressing an embryonic stem cell phenotype,

wherein the undifferentiated chicken cells:

(i) are derived from the chicken primordial germ cells isolated from the chicken embryo;

(ii) are smaller than the chicken primordial germ cells; and

(iii) form one or more colonies of tightly packed undifferentiated chicken cells expressing an embryonic stem cell phenotype.

47. The sustained culture of claim 44 wherein the preconditioned feeder matrix comprises cells that have been isolated from the gonad of a chicken embryo later than stage 14 according to the Hamburger & Hamilton staging system.

48. The sustained culture of claim 44 wherein the preconditioned feeder matrix comprises cells that have been isolated from the genital ridge of a chicken embryo later than stage 14 according to the Hamburger & Hamilton staging system.

53. The sustained culture of claim 44 wherein the embryonic stem cell phenotype is maintained for at least one month.

54. The sustained culture of claim 44 wherein the embryonic stem cell phenotype is maintained for at least two months.

58. The sustained culture of claim 44, wherein the undifferentiated chicken cells maintain the embryonic stem cell phenotype when grown on the preconditioned fibroblast feeder matrix in the presence of the conditioned media for at least three days.

Prior art

The Examiner has rejected the claims based on:

Petitte et al.	U.S. Patent 5,340,740	Aug. 23, 1994
Petitte et al.	U.S. Patent 5,656,479	Aug. 12, 1997
Petitte et al.	U.S. Patent 5,830,510	Nov. 3, 1998
Ponce de Leon	U.S. Patent 6,156,569	Dec. 5, 2000

Simkiss et al., *Infection of primordial germ cells with defective retrovirus and their Transfer to the Developing Embryo*, 16 4th World Congress on Genetics Applied to Livestock Production 111-114 (1990).

Petitte et al., *Production of somatic and germline chimeras in the chicken by transfer of early blastodermal cells*, 108 Development 185-189 (1990).

Ponce de Leon et al., *Recent advances in chicken primordial cell technology*, 21 Revista Brasileira de Reproducao Animal 96-101 (1997).

Naito et al., *Introduction of exogenous DNA into somatic and germ cells of chickens by microinjection into the germinal disc of fertilized ova*, 37 Molecular Reproduction and Development 167-171 (1994).

Chang et al., *Proliferation of chick primordial germ cells cultured on stroma cells from the germinal ridge*, 19 Cell Biology International 143-149 (1995).

Chang et al., *Production of germline chimeric chickens by transfer of cultured primordial cells*, 21 Cell Biology International 495-499 (1997).

Pain et al., *Long-term in vitro culture and characterisation of avian embryonic stem cells with multiple morphogenetic potentialities*, 122 Development 2339-2348 (1996).

The Rejections

- A. Claims 44, 47, 48, 51-54 and 56-58 stand rejected under 35 U.S.C. § 112, first paragraph as encompassing new matter.
- B. Claims 44, 47, 48, 51-54, and 56-58 stand rejected under 35 U.S.C. § 112, first paragraph as lacking enablement.
- C. Claims 44, 47, 48, 51-54, and 56-58 stand rejected under 35 U.S.C. § 112, second paragraph.
- D. Claims 44, 47, 48, 52-54, and 58 stand rejected under 35 U.S.C. § 102(b) as anticipated by Chang (1995).
- E. Claims 44, 47, 48, 52-54, and 58 stand rejected under 35 U.S.C. § 102(b) as anticipated by Chang (1997).
- F. Claims 44, 47, 48, 51-54, and 56-58 stand rejected under 35 U.S.C. § 102(e) as anticipated by one of Petite ‘740, Petite ‘479 or Petite ‘510.
- G. Claims 44, 47, 48, 51-54, and 56-58 stand rejected under 35 U.S.C. § 103(a) as obvious over Ponce de Leon ‘569 and Chang (1995).
- H. Claims 44, 47, 48, 51-54, and 56-58 stand rejected under the judicially-created doctrine of obviousness type double patenting over claims 1 and 8-10 of Petite ‘740 in view of Petite ‘740 and Chang (1995).
- I. Claims 44, 47, 48, 51-54, 56, and 57 stand rejected under the judicially-created doctrine of obviousness type double patenting over either claim 1 of Petite ‘479 or claim 1 of Petite ‘510 and Chang (1995).

A. 35 U.S.C. § 112, first paragraph, *New Matter rejection*

The Examiner's position is that

While "cells expressing an ESC phenotype" may be obtained and "cells of the invention can be cultured for at least one or two months," it is not readily apparent from those two sentences alone, taken with the rest of the paragraph, or taken with the rest of the specification, that applicants contemplated maintaining the ESC phenotype for one or two months.

(Ans. 5).

The Appellants contend that "one of ordinary skill in the art would understand after consideration of the specification as a whole that the specification discloses maintaining the embryonic stem cell phenotype for at least one or two months" (App. Br. 8). The Appellants further argue that

the specification discloses that the avian embryo cells of the present invention can be cultured for one or two months and further that the present invention relates to undifferentiated avian cells expressing an embryonic stem cell phenotype. Putting these two exemplary sections together clearly indicates that the "present invention" relates to "undifferentiated avian cells expressing an embryonic stem cell phenotype" that can be "cultured for at least one or two months".

(App. Br. 8). Appellants "submit that one of ordinary skill in the art would understand after consideration of the specification as a whole that the continuation of the cultures for one or two months relates to the sustained culture of the undifferentiated cells" (App. Br. 11).

In view of these conflicting positions, we frame the new matter issue before us as follows:

Would an ordinary artisan have interpreted the Specification as providing descriptive support for culturing chicken embryonic stem cells for one to two months?

Findings of Fact

1. “[A]vian cells give rise to nests or colonies of cells exhibiting an embryonic stem cell phenotype” (Spec. 13, l. 24 to 14, l. 1).
2. “The avian embryo cells of the present invention can be cultured for at least one or two months as is typical for a primary cell culture, which is significantly greater than the usual two week life of primary cultures of cells from an unincubated avian embryo” (Spec. 14, ll. 4-7).
3. The first sentence following the “Summary of the Invention” states “A method of producing a sustained culture of undifferentiated avian cells expressing an embryonic stem cell phenotype is disclosed” (Spec. 3, ll. 18-19).
4. “Accordingly, it is an object of the present invention to provide a novel process for the culturing of undifferentiated avian cells expressing an embryonic stem cell phenotype.” (Spec. 4, ll. 21-23).
5. According to the Specification:
It is another object of the present invention to provide a process for the culturing of undifferentiated avian cells expressing an embryonic stem cell phenotype from avian cells comprising primordial germ cells. It is a further object of the present invention to provide a feeder matrix for use in preparing a culture of undifferentiated avian cells expressing an embryonic stem cell phenotype using avian primordial germ cells. It is yet a further object of the present invention to characterize an optimal number of avian cells comprising

primordial germ cells for use in establishing a culture of undifferentiated avian cells expressing an embryonic stem cell phenotype.

(Spec. 5, ll. 1-10).

6. Each of the original independent claims includes the limitation “Undifferentiated avian cells expressing an embryonic stem cell phenotype” (see Spec. 25, 27, 29, original independent claims 1, 19, 35).

Discussion of 35 U.S.C. § 112, first paragraph New Matter rejection

We note that the Examiner has indicated that currently only claims 53 and 54 are rejected as incorporating new matter (Ans. 37). It is the Examiner's “initial burden [to] present [] evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims”. *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976). The proscription against the introduction of new matter in a patent application (35 U.S.C. 132 and 251) serves to prevent an Applicant from adding information that goes beyond the subject matter originally filed. *In re Rasmussen*, 650 F.2d 1212, 1214 (CCPA 1981).

We agree with Appellants that the Specification provides an adequate basis for the limitation at issue. Each time the Specification discusses the cells of the invention, the Specification states that the inventive cells have an embryonic stem cell phenotype (FF 3-6). When the Specification discusses the long term cultures at page 14, it refers to the cells as “avian embryo cells of the present invention” (FF 1-2, Spec. 14, l. 4). The Specification distinguishes these avian embryo cells of the present invention from both primary cell culture of incubated avian embryo and from primary cultures of unincubated avian embryos (see Spec. 14, ll. 1-7). The skilled artisan would

have recognized that when the Specification referred to cells of the present invention as being capable of culture for one to two months, these cells necessarily have the phenotype of the cells of the invention, which are repeatedly identified as having an embryonic stem cell phenotype (FF 1-6). Consequently, the skilled artisan would have concluded that there is descriptive support for claims 53 and 54 in the original Specification (*see* FF 1-6).

The written description rejection of the claims 53-54 under 35 U.S.C. § 112, first paragraph for new matter is reversed.

B. 35 U.S.C. § 112, first paragraph Enablement rejection

The Examiner's position is that "the specification, while being enabling for a culture comprising chicken ES cells does not reasonably provide enablement for a culture wherein ES cells are maintained for one or two months" (Ans. 6). The Examiner, in addition to relying upon references previously cited, appears to have further cited a paper by Van de Levoir, which was not cited in the Final Rejection and is not listed in the Evidence Relied Upon section of the Answer. Because this paper was not timely cited to Appellants and Appellants have not had an adequate opportunity to respond to it, we will not consider this reference further.

Appellants argue regarding the enablement rejection that the "one or two months" limitation only appears in claims 53 and 54, and therefore "it does not appear that the instant rejection is intended to be, or in fact can properly be, applied to claims 44, 47, 48, 51, 52, and 56-58" (App. Br. 12).

Appellants argue that "chicken PGCs do not have an ES cell phenotype as that phrase is employed in the instant claims" (App. Br. 13).

Appellants contend that the prior art culture conditions “do not inform the skilled artisan concerning how to culture undifferentiated cells derived from PGCs for one or two months because the cells of the instant claims are not PGCs” (App. Br. 13). Appellants also argue “that Ponce de Leon 1997 does not disclose any somatic chimeras, and thus the Examiner’s assertion that Ponce de Leon 1997 discloses chicken PGCs capable of producing somatic and germline chimeras reflects a[n] inaccurate understanding of Ponce de Leon 1997” (App. Br. 16).

In view of these conflicting positions, we frame the enablement issue before us as follows:

Does Appellants’ Specification, in concert with the prior art, enable culture of undifferentiated chicken cells expressing an embryonic stem cell phenotype where the embryonic stem cell phenotype is maintained for one or more months?

Findings of Fact

Breadth of the Claims

7. Claim 44 is drawn to a “sustained culture of undifferentiated chicken cells expressing an embryonic stem cell phenotype”; the claim does not require the phenotype to be maintained for any specific length of time (Claim 44).

8. Claim 53 is drawn to the sustained culture “wherein the embryonic stem cell phenotype is maintained for at least one month” (Claim 53).

9. Claim 54 is drawn to the sustained culture “wherein the embryonic stem cell phenotype is maintained for at least two months” (Claim 54).

Presence of Working Examples

10. “Gonadal cells were cultured on STO feeder layers for 3-5 days and stained with anti-SSEA-1. The number of single SSEA-1 positive PGCs and the number of SSEA-1 positive colonies were examined at day 0, 1, 3 and 5 of culture” (Spec. 20, ll. 10-13).

11. The Specification shows no examples of cells which were cultured more than 5 days (*see* Spec. 19-22).

Amount of Direction or Guidance Presented

12. “The avian embryo cells of the present invention can be cultured for at least one or two months as is typical for a primary cell culture, which is significantly greater than the usual two week life of primary cultures of cells from an unincubated avian embryo” (Spec. 14, ll. 4-7).

13. The Specification provides guidance on cofactors, media, feeder cells and starting cell material but provides no guidance on which cofactors, media, feeder cells or starting material will permit culture for 1 or 2 months (*see* Spec. 12-14).

State of the Prior Art and Unpredictability of the Art

14. “We have been unable so far to maintain clonal growth of CEC [chicken embryonic cells], which could suggest that some specific avian growth factors are necessary and produced by the blastodermal cells themselves” (Pain 2346, col. 2).

15. Pain obtained the cells from stage 9-11 embryos (*see* Pain 2340, col. 1).

16. Pain obtained cells from the blastoderm, not the embryonic genital ridge or gonad (*see* Pain 2340, col. 1).

17. Pain demonstrated that cells from a 7-day old culture functioned *in vivo* as ES cells (*see* Pain 2344, col. 2).

18. “By Stage XII, the hypoblast, which induces the formation of the primitive streak [] has started to differentiate suggesting that cells taken from this stage of embryonic development are less likely to be pluripotent” (Petitte (Development) 187-188).

19. “Long term culture systems for chicken ES and PGC have been relatively difficult to establish” (Ponce de Leon (1997) 98, col. 2).

20. “The long term ES culture system remains to be tested for pluripotency and germ line transmission” (Ponce de Leon (1997) 98, col. 2).

21. “We have also transfer[red] PGCs that have been maintained in culture for 25 days to five recipient embryos” (Ponce de Leon (1997) 100, col. 2).

22. Chang teaches that PGCs may be cultured for 5 days (*see* Chang (1997) 496, col. 2).

23. Petitte ‘510 states “[t]he culture of cells from the unincubated embryo has been more difficult and under reported conditions such cells do not survive beyond two weeks” (Petitte ‘510, col. 1, ll. 63-66).

Quantity of Experimentation necessary

24. “None of the cell feeder layers evaluated in this study improved the long term culture conditions of the PGCs. None of the growth factors

alone, at any of the concentrations studied, was able to sustain PGCs in vitro without differentiation” (Ponce de Leon (1997) 100, col. 2).

25. “A significant problem with all of these methods is the fact that long term culture systems for chicken ES and PGC have been relatively difficult to establish. To the best of the inventors’ knowledge, it is believed that the longest avian PGCs have been cultured with the successful production of chimeric birds is less than 5 days (Ponce de Leon ‘569, col. 2, ll. 41-46).

26. Ponce de Leon ‘569 teaches that culture using the novel method may extend up to 25 days (*see* Ponce de Leon ‘569, col. 4, ll. 42-49).

27. “Few or no attempts have been made to date regarding the culture of embryonic stem cells from avian embryos. The main reason for this is that it is very difficult to establish a continuous line of chicken cells without viral or chemical transformation and most primary chicken lines do not survive beyond 2-3 months. The culture of cells from unincubated embryo has been more difficult and under reported conditions such cells do not survive beyond two weeks” (Petitte ‘510, col. 1, ll. 58-66).

Discussion of 35 U.S.C. § 112, first paragraph Enablement rejection

The law is well settled that enablement must be commensurate in scope with the claimed invention. *See, e.g., Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1379 (Fed. Cir. 2007); *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). A single embodiment may be sufficient, if that teaching combined with the knowledge of the skilled artisan would enable the full scope of the claim. *See Johns Hopkins Univ. v. Cellpro Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998). However, in this case, in spite of the

well-recognized challenges in culturing avian embryonic stem cells, no working example of cells cultured longer than 5 days is disclosed (FF 7-11).

We analyze the scope of enablement using the factors discussed in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *In re Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

858 F.2d at 737. Applying the *Wands* analysis, we conclude that the Examiner has provided a prima facie case supporting the scope of enablement rejection with respect to claims 53 and 54. The cited prior art indicates that a large quantity of experimentation is required in order to maintain a culture of avian cells with an embryonic stem cell phenotype for one month or longer (FF 24-27). Ponce de Leon '569 exemplifies this evidence, commenting that a "[s]ignificant problem with all of these methods is the fact that long term culture systems for chicken ES and PGC have been relatively difficult to establish" (Ponce de Leon '569, col. 2, ll. 41-46).

The prior art also recognizes that significant direction or guidance is required in order to culture avian cells with embryonic cell phenotypes for one month or longer (*see* FF 14, 23-25, 27). However, the Specification does not provide guidance on factors necessary to culture avian cells for one

or more months (FF 12-13). In addition, the Specification lacks any working examples of cultures which exceed five days (FF 10-11).

The prior art is replete with discussions regarding the difficulties and unpredictability in culturing avian cells, particularly cells with embryonic stem cell phenotypes (FF 14-23). Even those references which purport to demonstrate culture for long periods differ from the claimed invention in significant ways, for example culturing dorsal aorta embryonic cells from stage 13-14 embryos rather than embryonic genital ridge or gonad cells from stage 15 or later embryos as required by the claim (*see* Ponce de Leon ‘569, col. 7, ll. 43-54). Appellants even argue that the cell types used by Ponce de Leon and others “do not inform the skilled artisan concerning how to culture undifferentiated cells derived from PGCs for one or two months because the cells of the instant claims are not PGCs” (App. Br. 13).

The prior art demonstrates that a large quantity of experimentation is necessary to culture avian embryonic cells (FF 24-27). The required experimentation is not characterized as routine, but rather the “culture of cells from the unincubated embryo has been more difficult and under reported conditions such cells do not survive beyond two weeks” (Petitte ‘510, col. 1, ll. 63-66). In concord, “[l]ong term culture systems for chicken ES and PGC have been relatively difficult to establish” (Ponce de Leon (1997) 98, col. 2).

We recognize that the skill in this art is at a high level. The remaining *Wands* factors support a conclusion of undue experimentation with respect to claims 53 and 54. These claims require one month or more of culture while retaining the embryonic stem cell phenotype, but there are no working

examples of culture beyond five days, no guidance in the Specification on culture for more than five days and the prior art supports the conclusion that such culture of cells retaining an embryonic stem cell phenotype requires a large quantity of unpredictable experimentation (FF 7-27).

We reject Appellants' argument that the prior art references cited are irrelevant to the enablement of the current claims because they are not necessarily drawn to embryonic stem cells (App. Br. 13-16). Most of the cited prior art references are attempting to generate avian embryonic stem cells and the success or failure of these references to do so is significantly relevant to Appellants' claims (FF 14-27). Appellants' detailed analysis of the Simkiss reference does not address the issue of the unpredictability in culturing avian cells for extended periods of time but simply argues whether PGCs may function to produce somatic chimeras (App. Br. 13-15). However, Ponce de Leon recognizes that "[t]o be useful, a PGCs culture system would require to allow transfection and selection of PGCs while maintaining the PGC ability to migrate to the gonads, unless chicken PGCs revert to the ES cell phenotype as it occurs with mouse PGCs" (Ponce de Leon 101, col. 1). Appellants' argument on the issue of whether PGCs can function as embryonic stem cells notwithstanding, there is no evidence presented either way other than speculation by Ponce de Leon. The strong prior art showing of the difficulty in culturing avian cells from the embryo for extended periods of time is the evidence which supports the scope of enablement rejection (FF 14-27).

We also reject Appellants' arguments regarding the issue of culture conditions for the embryonic stem cells (App. Br. 17). We think that

Appellants misapprehend the issue, which is that there is no teaching or working example in the Specification on how to culture embryonic stem cells for periods of one month or more (FF 10-13). Appellants' arguments, which suggest that the inability of the prior art to culture avian PGCs for extended periods of time, is irrelevant is simply not persuasive. Even if we accept Appellants' position on its face, if culture of one lineage of avian embryonic cells is unpredictable and requires unpredictable combinations of growth factors, this unpredictability is strongly supportive of a conclusion that culture of a different lineage of avian cells (the embryonic stem cell lineage) which lineage is defined solely functionally would also be unpredictable in the absence of specific guidance or examples teaching modes of extended culture of the embryonic stem cell lineage.

Based on our interpretation and findings and those of the Examiner, we therefore conclude that there is substantial evidence which supports the conclusion that the claims are not enabled for culturing embryonic stem cells for periods of one month or more. The rejection of claims 53 and 54 under 35 U.S.C. § 112, first paragraph for lack of enablement is affirmed.

However, the rejection of claims 44, 47, 48, 51, 52 and 56 of the same basis is reversed because those claims do not require maintaining the embryonic stem cell phenotype for at least one month. *Cf. In re Cortright*, 165 F.3d 1353, 1358-59 (Fed. Cir. 1999) (Claims to a method of "restoring hair growth" that encompassed, but did not require, achieving a full head of hair were held to be enabled by evidence showing three-fold increase in hair number, filling-in, and fuzz). Just as the claims in *Cortright* did not require achieving growth of a full head of hair, instant claim 44 does not require

achieving a sustained culture of undifferentiated chicken cells that maintain an embryonic stem cell phenotype indefinitely.

C. 35 U.S.C. § 112, second paragraph indefiniteness rejection

The Examiner's position is that the "cells encompassed by the phrase 'undifferentiated chicken cells expressing an embryonic stem cell phenotype' are unclear" (Ans. 11). The Examiner argues that because the definition in the Specification defines the cells as having a large nucleus, prominent nucleolus and little cytoplasm without defining what "large", "prominent" or "little" mean, the claim is indefinite (Ans. 11). The Examiner concedes that the skilled artisan knew that "ES cells were defined as cells having the ability to become both somatic and germ cells upon being introduced into an avian embryo" (Ans. 11).

The Examiner also argues that the claims are indefinite because "PGCs isolated from an embryo later than stage 14 as claimed are not distinguished from PGCs isolated from a stage 10 or stage 14 embryo" (Ans. 13).

The Appellants contend that the embryonic cells "are derived from the chicken primordial germ cells (PGCs) isolated from a chicken embryo at a stage later than stage 14 according to the Hamburger & Hamilton staging system and are smaller than the chicken primordial germ cells so isolated." (App. Br. 20). The Appellants conclude that the ordinary artisan would recognize that cells expressing the "embryonic stem cell phenotype are morphologically distinguishable from PGCs" (App. Br. 21). Appellants also

point out that the Specification recognizes that embryonic germ cells and embryonic stem cells are phenotypically the same (*see* App. Br. 22).

Regarding the staging issue,

Appellants respectfully submit that there are two main art-recognized staging systems, the Eyal-Giladi and Kochav (EG&K; from Eyal-Giladi and Kochav, 1976, *Dev. Biol.* 49(2):321-37) staging system and the Hamburger and Hamilton (H&H from Hamburger & Hamilton, 1951, *J Morphol* 88:49-92) staging system. The former uses Roman numerals, and the latter Arabic numerals.

(App. Br. 24.) Appellants then argue “the Examiner is equating PGCs with the undifferentiated cells of the claimed sustained cultures” (App. Br. 25).

In view of these conflicting positions, we frame the indefiniteness issues before us as follows:

(1) Is the phrase “‘undifferentiated chicken cells expressing an embryonic stem cell phenotype’ indefinite in view of the definition in the Specification and the prior art?

(2) Are the claims indefinite because stage 10 and stage 14 PGCs are not distinguishable from one another?

Discussion of 35 U.S.C. § 112, second paragraph indefiniteness rejections

The Federal Circuit has noted that “The standard of indefiniteness is somewhat high; a claim is not indefinite merely because its scope is not ascertainable from the face of the claims.” *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1342 (Fed. Cir. 2003). Rather, “[a] claim is indefinite if, when read in light of the specification, it does not reasonably apprise those skilled in the art of the scope of the invention.” *Id.*

We disagree with the Examiner and conclude that the phrase “undifferentiated chicken cells expressing an embryonic stem cell phenotype” is reasonably definite. The phrase must be read in light of the specific definition in the Specification that teaches some broad structural constraints regarding the relative sizes of the nucleus, nucleolus and cytoplasm (Spec. 9). The phrase must also be read using the knowledge of the skilled artisan regarding the functional constraint that embryonic stem cells are capable of forming both somatic and germ cell chimeras (*see* Ans. 11). This knowledge provides sufficient information to apprise the skilled artisan of the scope of the phrase in the context of the invention. “Even if it is a formidable task to understand a claim, and the result not unanimously accepted, as long as the boundaries of a claim may be understood it is ‘sufficiently clear to avoid invalidity [for] indefiniteness.’” *Invitrogen Corp. v. Biocrest Mfg.*, 424 F.3d 1374, 1383 (Fed. Cir. 2005). Here, the boundaries of the embryonic stem cells are susceptible to routine experimentation regarding their functional characteristics, which is sufficient to avoid indefiniteness. An ordinary practitioner could determine whether specific cells were embryonic stem cells by viewing their morphological features and determining whether the cells were capable of giving rise to both somatic and germ cell chimeras (*see* App. Br. 22-23, Ans. 11).

We also disagree with the Examiner that PGCs isolated from an embryo later than stage 14 are not distinguished from PGCs isolated from a stage 10 to stage 14 embryo (*see* Ans. 13). In fact, the cells are clearly distinguished by their process of making, since the ordinary practitioner, in generating the cells, can determine which well recognized stage was used as

the source material (*see* App. Br. 24). *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed.Cir.1986) (“if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more”).

We therefore reverse the rejections of claims 44, 47, 48, 51-54 and 56-58 for indefiniteness in light of this Specification.

D. 35 U.S.C. § 102(b) rejection over Chang (1995)

The Examiner contends that

Chang (1995) isolated the germinal ridge of day 5 embryos (stage 27-28) and cultured the cells for 4 or 5 days (pg 143, "Preparation of germinal ridge and culture of stroma cells"; pg 146, Fig. 2 and caption for Fig. 2). The germinal ridge cells comprised stromal cells (pg 144, line 6) and PGCs (last sentence on pg 144: "The feeder layer derived from GRs must contain intrinsic PGCs").

(Ans. 14). The Examiner notes that the USPTO “does not have the means to compare the size of the germinal ridge PGCs in culture after 5 days to the PGCs contained in the original germinal ridge isolate” (Ans. 16). The Examiner further notes the USPTO “does not have the means to compare the size of the blood PGCs in culture after 5 days to the PGCs contained in the original blood isolate” (Ans. 18). The Examiner also argues “the limitation of isolating PGCs and stromal cells together does not bear patentable weight because PGCs and stromal cells isolated separately then mixed together have the same structure and function as those isolated together” (Ans. 17).

With regard to claims 53 and 54, the Examiner argues “the structure and function of a culture in which the ES cell phenotype is maintained for 5 days is equivalent to a culture in which the ES cell phenotype is maintained for one or two months” (Ans. 16). For claim 58, the Examiner states that the “germinal ridge cells inherently comprise fibroblasts as in claim 58 because the cells were grown in fibroblast growth factor (pg 144, first full paragraph)” (Ans. 17).

Appellants contend that

Chang (1995) does not disclose the production of a sustained culture comprising undifferentiated chicken cells, wherein the undifferentiated chicken cells (i) are derived from chicken PGCs isolated from the genital ridge or gonad of a later than stage 14 embryo, (ii) are smaller than the chicken PGCs so isolated; and (iii) form one or more colonies of tightly packed undifferentiated chicken cells that express an embryonic stem cell phenotype.

(App. Br. 16). Appellants conclude that “Chang (1995) does not disclose a change in either the phenotype of or the behavior of the isolated cells (i.e., the PGCs)” (App. Br. 16).

Appellants also argue claims 53, 54 and 58, stating Chang (1995) fails to “disclose maintaining the undifferentiated state for at least one (claim 53) or two (claim 54) months or maintaining the embryonic stem cell phenotype when the cells are grown on the preconditioned fibroblast feeder matrix in the presence of the conditioned media for at least three days (claim 58)” (App. Br. 26-27).

In view of these conflicting positions, we frame the issues before us as follows:

(1) Does the sustained culture of cells disclosed by Chang (1995) inherently comprise undifferentiated chicken cells expressing an embryonic stem cell phenotype thereby inherently anticipating the invention?

(2) Are avian embryonic stem cells cultured for one or two months inherently identical to avian embryonic cells cultured for five days thereby anticipating claims 53 and 54?

(3) Does Chang (1995) directly or inherently teach that culture of the avian embryonic stem cells on fibroblast feeder cells maintains the ESC phenotype thereby anticipating claim 58?

Findings of Fact

28. Chang (1995) discloses a sustained culture of chicken cells for 5 and 10 days (*see* Chang (1995) 145, col. 1).

29. Chang (1995) teaches a conditioned feeder matrix, specifically “stroma cells derived from 5-day-old germinal ridge in Medium 199 supplemented with 10% FBS, human IGF-1, bovine FGF-b and murine LIF” (Chang (1995), abstract).

30. Chang (1995) teaches conditioned media noting that
For culture of GR stroma cells and PGCs, we used Medium 199 based on Earl's balanced salt solution (GIBCO Oriental Co.) supplemented with 10% FBS, 10 ng/ml of insulin-like growth factor-1 (IGF-1, Gro Pep Pty. Ltd.), 10 ng/ml of basic fibroblast growth factor (FGF-b, PEPRO TECH Inc.) and 10 units/ml of murine leukemia inhibitory factor (LIF, ESGRO Co.)

(Chang (1995) 144, col. 1).

31. Chang (1995) discloses a mixture of chicken primordial germ cells and chicken stromal cells isolated from the embryonic genital ridge of a

chicken embryo (*see* Chang (1995) 143, col. 2) and PGCs from 5 day old embryos are inherently from a stage later than stage 14 (*see* Chang (1997) abstract).

32. Chang (1995) teaches that “[i]ntrinsic PGCs in the 5-day embryonic germinal ridge were observed loosely attached to the stroma cells and they also increased 3.8 fold during culture for 4 days” (Chang (1995), abstract).

33. Chang (1995) teaches that after five days in culture, some of the PGCs derived from 5 day embryonic germinal ridge grew as an aggregate (Chang (1995) 145, fig. 2, panel D and figure legend).

34. Chang (1995) discloses an aggregate of chicken cells in figure 2, panel D, in which some of the cells are smaller than other chicken primordial germ cells (*see* Chang (1995) 145, fig. 2, panel D).

35. Chang (1995) does not discuss, nor do the figures clearly disclose, the relative sizes of the nucleus, nucleolus or cytoplasm of the chicken PGCs (*see* Chang (1995) 145, fig. 2).

36. Chang (1995) does not disclose culture of the cells for periods exceeding 10 days (*see* Chang (1995) 145, col. 1).

37. Chang (1995) does not teach the use of a fibroblast feeder cell matrix (*see* Chang (1995) 144, col. 1, where stroma cells were used as the feeder layer).

Discussion of 35 U.S.C. § 102(b) rejection over Chang (1995)

We agree with the Examiner on the first issue that Chang (1995) supports a *prima facie* case of anticipation. Chang (1995) teaches a sustained culture of cells in which the chicken primordial germ cells from the

embryonic genital ridge were isolated from an embryo at a stage later than stage 14 and which were cultured in conditioned media on a preconditioned feeder matrix including chicken stromal cells (FF 28-31). Chang (1995) further teaches that the cells were aggregated and differed in size (FF 32-34). The only feature identified by the Specification on which Chang (1995) is silent is the relative sizes of the nucleus, nucleolus and cytoplasm (see Spec. 9, ll. 4-5).

We agree with the Examiner regarding the sizes of the putative embryonic stem cells in Chang (1995) that the USPTO “does not have the means to compare the size of the germinal ridge PGCs in culture after 5 days to the PGCs contained in the original germinal ridge isolate” (Ans. 16). *See In re Schreiber*, 128 F.3d 1473, 1478 (Fed. Cir. 1997)(“Where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.”) Appellants have not provided any evidence that the Chang (1995) cells, which are from an identical source at an identical stage and grown on identical feeder cells as compared to Appellants’ claims differ in any way from the sustained culture of embryonic stem cells claimed by Appellants.

We reject Appellants’ argument that Chang (1995) does not teach “a culture that includes undifferentiated derivatives of PGCs that are smaller than PGCs and form tightly packed colonies” (App. Br. 26). Chang (1995) expressly teaches cells derived from PGCs which form aggregates and some

of which are smaller than others but does not disclose whether they have the embryonic stem cell phenotype (FF 33-34, 36). “Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product.” *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977).

The Examiner has provided substantial evidence showing that the claimed culture of cells is identical, or at least substantially identical, to the cells disclosed by Chang (1995). The only contrary evidence provided by Appellants is the Petite Declaration (filed Oct. 6, 2005). In this Declaration, Dr. Petite asserts that the claimed cells are derived from PGCs but are not PGCs (Petite Dec. 2, No. 6). Dr. Petite also asserts that PGCs differ in nucleus to cytoplasm ratio and in aggregation properties (Petite Dec. 3, No. 8). Dr. Petite concludes that the claimed cells are not PGCs (Petite Dec. 3, No. 8).

The Petite Declaration has provided no substantive evidence that the Chang (1995) cells do not inherently comprise cells with an embryonic stem cell phenotype (*see* Petite Dec. 1-4). Dr. Petite has not performed a direct comparison of the cells isolated by Chang (1995) with the claimed ES cells and shown any structural or functional difference (*see* Petite Dec. 1-4). Dr. Petite did not analyze the Chang (1995) data and figures to determine whether the cells shown were different (*see* Petite Dec. 1-4). Given that the source of the cells is the same, from the same cell stages, cultured with stromal feeder cells and similar culture conditions (*see* FF 28-34), we are not

persuaded that Dr. Petite has asserted any facts which dispute the case for Chang (1995) to inherently comprise the claimed cells.

Consistent with the decisions of *Schreiber* and *Best*, we affirm the anticipation rejection over Chang (1995) for claims 44, 47, 48, 52, and 56.

We disagree with the Examiner on the second issue regarding whether avian embryonic cells cultured for one or two months are inherently identical to avian embryonic cells cultured for five days. Chang (1995) does not culture the PGCs for more than 10 days (FF 35). The Examiner finds that “[c]ulturing the PGCs for one or two months does not alter the structure or function of the culture” (Ans. 16). However, the references cited by the Examiner for the enablement rejection disagree with this conclusion. For example, Ponce de Leon (1997) notes that “about 48 hours after collection, PGCs clump together and start dividing as . . . is evident by the growth in size of the clump and the number of cells observed after trypsin dissociation of the clump. Only PGCs that form clumps survive, all others die” (Ponce de Leon (1997) 101, col. 1). While this observation supports the anticipatory nature of Chang (1995) discussed above, it also shows that extended culture of the PGCs results in changes in the cells, and opposes the Examiner’s conclusion that extended culture does not alter the cells. In concord, Pain notes “we may imagine that germ-line precursors are lost preferentially from the culture” (Pain 2346, col. 2). This supports a conclusion that extended culture of the chicken cells may alter the types of cells present in culture or the characteristics of the surviving cells.

We therefore reverse the Chang (1995) anticipation rejection with regard to claims 53 and 54.

We also disagree with the Examiner with regard to the third issue of whether Chang (1995) teaches the use of fibroblasts as a feeder matrix for the embryonic stem cells. Chang (1995) does not teach culture on fibroblasts (*see* FF 37). The Examiner argues that the “germinal ridge cells inherently comprise fibroblasts as in claim 58 because the cells were grown in fibroblast growth factor (pg 144, first full paragraph)” (Ans. 17).

This inherency argument is unconvincing because there is no evidence that simply culturing the stroma cells in the presence of fibroblast growth factor will convert the stroma cells into fibroblasts “‘Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.’” *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981). In fact, Chang (1995) also adds insulin-like growth factor and murine leukemia inhibitory factor (Chang (1995) 144, col. 1). Just as the presence of insulin-like growth factor in the media does not inherently mean that the stroma cells will differentiate into pancreatic β -cells, so too, in the absence of direct evidence, the presence of fibroblast growth factor does not inherently require that the stroma cells will differentiate into fibroblasts. Unlike the inherency argument for claim 44, the inherency argument for claim 58 does not rest on products that are identical in composition, insofar as can be determined. The fibroblast feeder layer of claim 58 is not disclosed by the rejection and there is no substantive evidence to support the Examiner’s contention that fibroblast growth factor will inherently convert the stroma feeding layer into fibroblasts (*see* FF 37).

We therefore reverse the Chang (1995) anticipation rejection with regard to claim 58.

E. 35 U.S.C. § 102(b) rejection over Chang (1997)

The issues of the Chang (1997) paper are substantially the same as those of the Chang (1995) paper. As argued by Appellants “Chang (1997) does not support the instant anticipation rejection for precisely the same reasons that are outlined immediately hereinabove with respect to Chang (1995)” (App. Br. 27).

Findings of Fact

38. Chang (1997) expressly teaches that the PGCs were derived from stage 27, which is later than stage 14 of the Hamburger & Hamilton staging system (Chang (1997) 496, col. 1).

39. Chang (1997) teaches that the PGC cells were capable of forming germline chimeras (Chang (1997) 496, col. 2).

Discussion of 35 U.S.C. § 102(b) rejection over Chang (1997)

We agree with the Examiner that Chang (1997) anticipates claims 44, 47, 48, 52, and 56 for the same reasons as discussed above. The Chang (1997) reference incorporates the teachings of the Chang (1995) reference in its method of generating a culture of PGCs (Chang (1997) 496, col. 1) “The GRSCs were prepared and cultured according to the method of Chang et al (1995a).”

However, the Chang (1997) reference makes explicit two points about which Chang (1995) is silent. Chang (1997) makes crystal clear that the five day embryo is from stage 27, which is clearly a stage later than stage 14 (FF 38). Chang (1997) also provides evidence that the cultured avian PGCs are inherently capable of at least one of the requirements of an embryonic stem cell phenotype, which is to form germline chimeras (FF 39).

As above, Chang (1997) expressly teaches a sustained culture of cells derived from the embryonic genital ridge of chicken embryos at stage 27 that are placed into conditioned media on a stromal cell feeder matrix which are derived from PGCs and which are capable of forming germline chimeras (Chang (1997) 496, col. 1 and FF 37-38). “Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product.” *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). The Examiner has met the burden of a prima facie case of anticipation with identical or substantially identical products, but Appellants have not provided any actual evidence that the cultured cells of Chang (1997) do not inherently have an embryonic stem cell phenotype. For the same reasons as given above, we do not find the Petite Declaration persuasive.

Consistent with the decisions of *Schreiber* and *Best*, we affirm the anticipation rejection over Chang (1997) for claims 44, 47, 48, 52, and 56.

However, as above, we disagree with the Examiner on the second issue regarding whether cells grown for one or two months are inherently identical to cells grown for five days as taught by Chang (1997). For the same reasons we discussed regarding Chang (1995), we conclude that Chang (1997) does not teach or suggest growth of cells for one or two months.

Similarly, we also disagree with the Examiner regarding whether the feeder cells in Chang (1997) are inherently fibroblasts. For the same reasons

we discussed regarding Chang (1995), we conclude that Chang (1997) does not teach the use of a fibroblast feeder cell matrix.

We therefore reverse the Chang (1997) anticipation rejection with regard to claims 53, 54, and 58.

F. 35 U.S.C. § 102(e) rejection over any of Petite '740, Petite '479 or Petite '510

The Examiner contends that

The process limitation of isolating PGCs and stromal cells together from the embryonic genital ridge or gonad from a chicken embryo at a stage later than stage 14 does not distinguish the cells from PGCs of whole stage X embryos mixed with stromal fibroblasts isolated from a 10-day old chick embryo. PGCs isolated from the germinal ridge or gonad of an embryo after stage 14 as claimed are not structurally and functionally distinct from the PGCs of whole stage X embryos taught by Petite.

(Ans. 45).

Appellants argue that the isolation of cells from the whole stage X embryo is not the same as those isolated from the genital ridge “because stage X embryos have neither a genital ridge nor a gonad. The chicken embryo at Stage X (i.e., a blastoderm stage) has not yet formed the three primary germ layers: ectoderm, mesoderm, and endoderm” (App. Br. 29). Therefore, the Appellants contend that “the Examiner’s assertion that genital ridge and/or gonadal stromal cells exist in a Stage X embryo is scientifically inaccurate” (App. Br. 29). Appellants separately argue that the Petite patents do not teach the use of a preconditioned feeder matrix as required by claims 47 and 48 (App. Br. 29).

We note that all three of these patents share an identical disclosure since the Petite '510 patent is a continuation of the Petite '479 patent which is a divisional of the Petite '740 patent. We will therefore focus on the Petite '740 patent.

In view of these conflicting positions, we frame the issue before us as follows:

Does the sustained culture of cells from a whole stage X embryo as disclosed by the Petite patents inherently comprise undifferentiated chicken cells expressing an embryonic stem cell phenotype thereby inherently anticipating the invention?

Findings of Fact

40. Petite '740 teaches "a sustained avian cell culture consisting essentially of undifferentiated avian cells having a large nucleus, a prominent nucleolus and little cytoplasm (an 'embryonic stem cell phenotype'") (Petite '740, col. 2, ll. 35-40).

41. Petite '740 teaches that the cells are "grown on the mouse fibroblast feeder layer" (Petite '740, col. 2, ll. 33-34).

42. Petite '740 teaches the use of a medium conditioned with leukemia inhibitory factor (Petite '740, col. 2, ll. 22-25).

43. Petite '740 teaches obtaining the cells from stages IX to XIV (Petite '740, col. 3, ll. 20-22).

44. Petite '740 exemplified growth of cells from stage X embryos for 23 passages (Petite '740, col. 7).

45. Petitte '740 never discusses stromal cells, primordial germ cells, or deriving cells from the embryonic genital ridge or gonads (Petitte '740, col. 1-8).

Discussion of 35 U.S.C. § 102(e) rejection over any of Petitte '740, Petitte '479 or Petitte '510

We agree with Appellants that isolation of cells from a cell source which does not have a genital ridge or gonads and which is drawn from a different stage of embryonic development than the claimed invention, does not inherently anticipate the claimed invention (FF 40-45). It is well settled that

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference.

Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991). The Examiner has presented no evidence to support the conclusion that cells derived from a whole stage X embryo would necessarily be the same as cells derived from the embryonic genital ridge or gonads of a stage 15 or later embryo. The court also notes that “[i]nherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” *Continental*, 948 F.2d at 1269. Unlike the Chang (1995) situation where all of disclosed elements are identical to the claimed invention, here many of the elements differ from those required by the claims.

We are not persuaded by the Examiner's reasoning that the process limitation of isolating PGCs and stromal cells together from the embryonic genital ridge or gonad from a chicken embryo at a stage later than stage 14 does not distinguish the cells from PGCs of whole stage X embryos mixed with stromal fibroblasts isolated from a 10-day old chick embryo.

(Ans. 45). While it is certainly possible that some of the cells from a stage X embryo will develop in vitro into the same type of cells as those derived from the genital ridge or gonads of a stage 14 embryo, the Examiner has not presented evidence or persuasive argument that this is probable or even likely (*see* FF 43-45).

We therefore reverse the anticipation rejections over the Petite '740, Petite '479 and Petite '510 patents with regard to claims 44, 47, 48, 51-54, and 56-58.

G. 35 U.S.C. § 103(a) rejection over *Chang (1995)* and *Ponce de Leon '569*

The Examiner states that "Ponce de Leon isolated PGCs from the dorsal aorta of stage XIV chicken embryos. The cells were cultured with complete medium, LIF, FGF, IGF and SCF for at least 25 days (col. 7, line 43 through col. 8, line 53)" (Ans. 24). The Examiner argues that the "PGCs described by Ponce de Leon are 'undifferentiated chicken cells expressing an embryonic stem cell phenotype' because they have a small nucleus, a prominent nucleolus and little cytoplasm as compared to other types of cells" (Ans. 25). The Examiner further contends that the "limitation of collecting PGCs from a the genital ridge or gonad of a chicken embryo at a

stage later than stage 14 does not distinguish the structure or function of the PGCs from those isolated from the blood of stage 14 embryos as described by Ponce de Leon” (Ans. 26).

The Examiner notes that Ponce de Leon does not teach stromal cells or a preconditioned fibroblast feeder matrix but relies upon Chang (1995) for the teaching of stromal cells (Ans. 27). The Examiner concludes that “it would have been obvious to one of ordinary skill in the art at the time the invention was made to culture PGCs isolated from the dorsal aorta as described by Ponce de Leon with stromal cells isolated from the germinal ridge of a chicken embryo at a stage later than stage 14 as described by Chang (1995)” (Ans. 27).

The Examiner also argues that the length of culture for claims 53 and 54 does not distinguish the cells of Ponce de Leon from the claimed invention (Ans. 27-28).

Appellants argue “that Chang (1995) does not disclose PGC-derived cells that are smaller than primordial germ cells and that form one or more colonies of tightly packed undifferentiated avian cells as recited in claim 44” (App. Br. 30). Appellants contend that Ponce de Leon ‘569 does not solve this deficiency because “at best the ‘569 Patent teaches a method of long term culturing of PGCs per se in a feeder-free culture with the addition of exogenous growth factors including LIF, bFGF, IGF, and SCF” (App. Br. 31). Appellants then note that the PGCs disclosed by Ponce de Leon ‘569 are not the same as the embryonic stem cells being claimed because they produce only germline chimeras, not somatic chimeras (App. Br. 32).

Appellants reiterate the same arguments discussed above regarding the Chang (1995) reference (App. Br. 32-33).

In addition, Appellants argue that neither reference teaches a preconditioned feeder matrix using gonad or genital ridge cells as required by claims 47 and 48 (App. Br. 33). Appellants further contend that because Ponce de Leon '569 teaches the use of four growth factors in the growth of the avian fibroblasts as feeder cells, this “teaches away from the generalized use of chicken fibroblasts as a feeder layer” (App. Br. 33). Also, Appellants argue that the references do not teach how to “produce cultures of such cells that maintain the undifferentiated state for at least one (claim 53) or two (claim 54) months, or when grown on a preconditioned fibroblast feeder matrix in the presence of the conditioned media for at least three days (claim 58)” (App. Br. 34).

In view of these conflicting positions, we frame the issues before us as follows:

(1) Would it have been obvious to culture the cells of Chang (1995) on the fibroblast feeder matrix of Ponce de Leon '569?

(2) Would it have been obvious based on Chang (1995) and Ponce de Leon '569 to culture avian embryonic stem cells for one or two months as required by claims 53 and 54?

Findings of Fact

We incorporate the facts found for Chang (1995) *supra*. We find the following facts for Ponce de Leon '569.

46. Ponce de Leon '569 discloses that “avian PGCs, preferably Gallinacea PGCs, and most preferably chicken PGCs can be maintained in

tissue culture for prolonged periods, in at least 14 days, more preferably at least 25 days and preferably longer” (Ponce de Leon ‘569, col. 4, ll. 42-47).

47. Ponce de Leon ‘569 cites to the Chang (1995) paper (erroneously dating it as 1992) and notes that “[m]ethods for isolation of primordial germ cells from donor avian embryos have been reported in the literature and can be effected by one skilled in the art” (Ponce de Leon ‘569, col. 4, ll. 62-66).

48. Ponce de Leon ‘569 “elected to isolate avian PGCs from chicken eggs which had been incubated for about 53 hours (stage 12-14 of embryonic development), removal of embryos therefrom, collection of embryonic blood from the dorsal aorta thereof and transferal thereof to suitable cell culture medium” (Ponce de Leon ‘569, col. 5, ll. 4-9).

49. Ponce de Leon ‘569 teaches that “feeder cells may also be useful. In particular, the use of fibroblasts, preferably avian fibroblasts, and most preferably Gallinacea fibroblasts (and still more preferably chicken fibroblasts) will provide for maintenance of PGCs in tissue culture provided that the four essential growth factors are present” (Ponce de Leon ‘569, col. 5, ll. 49-54).

Discussion of 35 U.S.C. § 103(a) rejection over Ponce de Leon ‘569 and Chang (1995).

Having affirmed the anticipation rejection of claims 44, 47, 48, and 52, based upon Chang (1995), we necessarily affirm these claims as obvious. *See In re Fracalossi*, 681 F.2d 792, 794 (CCPA 1982)(“evidence establishing lack of all novelty in the claimed invention necessarily evidences obviousness”). We note that the Examiner has withdrawn the rejection with regard to claims 51, 56 and 57.

With regard to claim 58, we reject Appellants' argument that the Ponce de Leon '569 patent does not motivate culture of cells "on a preconditioned fibroblast feeder matrix in the presence of conditioned media for at least three days" (App. Br. 34). Ponce de Leon '569 expressly teaches the growth of PGCs for in excess of three days (FF 46). Further, Ponce de Leon '569 refers to Chang (1995) as one mode of isolation of the PGCs (FF 47). Finally, Ponce de Leon '569 directly suggests the use of fibroblast feeder layers (FF 49). We find that an ordinary practitioner would have been motivated by Ponce de Leon '569 to isolate PGCs from the germinal ridge of embryos that are past stage 14 using the method of Chang (1995) since Ponce de Leon '569 directly references Chang (1995) regarding PGC isolation. We further find that the ordinary practitioner would have been motivated to use fibroblast feeder cells since Ponce de Leon '569 states "feeder cells may also be useful. In particular, the use of fibroblasts, preferably avian fibroblasts, and most preferably Gallinacea fibroblasts (and still more preferably chicken fibroblasts) will provide for maintenance of PGCs in tissue culture provided that the four essential growth factors are present" (Ponce de Leon '569, col. 5, ll. 49-54). The combination of Ponce de Leon '569's feeder cells with the PGCs of Chang (1995) is merely a "predictable use of prior art elements according to their established functions." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

We do not find Appellants' argument that Ponce de Leon '569 requires four growth factors to support a "teaching away" argument for claim 58, or for claims 47 and 48. This argument fails to appreciate the scope of Appellants' claims. Claims 47, 48, and 58 all utilize open claim

language. The transitional term “comprising” is “inclusive or open-ended and does not exclude additional, unrecited elements or method steps.” *Georgia-Pacific Corp. v. United States Gypsum Co.*, 195 F.3d 1322, 1327 (Fed. Cir. 1999). Therefore, Appellants’ use of the term “comprising” permits the presence of additional elements, such as the four essential growth factors of Ponce de Leon ‘569. Like our appellate reviewing court, “[w]e will not read into a reference a teaching away from a process where no such language exists.” *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1364 (Fed. Cir. 2006).

We affirm the 35 U.S.C § 103(a) rejection of claim 58 over Ponce de Leon ‘569 and Chang (1995).

We agree with Appellants that the prior art does not suggest the limitations of claims 53 and 54. While Ponce de Leon ‘569 does teach culturing PGCs for 25 days and suggests culturing the cells for indefinite periods, there is no reason to think that the PGCs of Ponce de Leon ‘569 are inherently identical to the claimed cells of Appellants (*see* Ponce de Leon ‘569, col. 6, ll. 21-29). The PGCs of Ponce de Leon ‘569 are derived from a different stage embryo (albeit the stage immediately preceding the stage claimed) and from a different cellular location in the embryo than the claims, the dorsal aorta rather than the genital ridge or gonads (FF 48).

The Examiner has presented no evidence to support the conclusion that cells derived from the dorsal aorta of a stage 14 embryo would likely or necessarily be the same as cells derived from the embryonic genital ridge or gonads of a stage 15 or later embryo. “Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result

from a given set of circumstances is not sufficient.” *Continental*, 948 F.2d at 1269. Unlike the Chang (1995) situation where all of disclosed elements are identical to the claimed invention, the PGCs of Ponce de Leon ‘569 differ from those required by claims 53 and 54 in their source in the embryo and in their cell stage. These differences defeat the inherency argument because it is at best possible that the isolated cells will be the same.

We reverse the 35 U.S.C § 103(a) rejection of claims 53 and 54 over Chang (1995) and Ponce de Leon ‘569.

H. Obviousness type Double Patenting rejection over Petite ‘740 and Chang (1995)

The Examiner argues that “[w]hile claim 1 of ‘740 requires isolating cells from a blastoderm prior to formation of the primitive streak, isolating cells from the genital ridge or gonad of an embryo at a stage later than stage 14 as now claimed does not distinguish the culture produced in the method of claim 1 of ‘740 from the culture now in claim 44” (Ans. 28).

Appellants contend

there is no motivation in the cited combination or in knowledge of the skilled artisan that would have led one of ordinary skill in the art to use PGCs isolated from the gonad or genital ridge of later than stage 14 embryos to produce sustained cultures of undifferentiated chicken cells as recited in the instant claims. At the time of filing, one of ordinary skill in the art would have believed that the PGCs located in these regions of an embryo at this stage were committed to terminal differentiation and thus unable to generate these cells.

(App. Br. 38).

In view of these conflicting positions, we frame the issue before us as follows:

Do claims 44, 47, 48, 51-54 and 56-58 define something that is an obvious variant of what is claimed in claims 1 and 8-10 of Petite ‘740 in view of Chang (1995)?

Discussion of Obviousness Double Patenting rejection over Petite ‘740 and Chang (1995)

In obviousness-type double patenting rejections, one must determine whether the claims of the later filed application would have been obvious in view of the claims of the earlier patent. *In re Goodman*, 11 F.3d 1046, 1052, (Fed. Cir. 1993).

We think that substitution of the Chang (1995) cells for those claimed in the Petite ‘740 patent represents an unpredictable variation, not an obvious variant. We disagree with the Examiner that the use of different sources of cells derived from different stages of embryo development will not result in a different culture of avian cells (*see* Answer 28). Just as “[i]f a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability”, when the variation is unpredictable, the result is likely unobvious. *See KSR v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007). Claim 1, the broadest independent claim, is limited to “collecting avian cells from an avian blastoderm prior to formation of the primitive streak” (Petite ‘740, col. 8, ll. 37-38). This is substantially different than claim 44 of the instant application, in which the PGCs and stromal cells “are isolated together from the embryonic genital ridge or gonad from a chicken embryo at a stage later than stage 14”.

Substitution of the cells of Chang (1995) for those of claims 1 and 8-10 of Petite '740 would have been expected to yield unpredictable results by an ordinary practitioner. We note that Appellants argue regarding the substitution of the Chang (1995) cells for those in the Petite '740 claims that "a skilled artisan attempting to produce a culture of undifferentiated cells would not employ cells believed to be committed to terminal differentiation" (App. Br. 37). We need not fully agree with Appellant's position to recognize that there would be an expectation of significant unpredictability in the substitution of cells which differ in stage, in source and in culture conditions.

We therefore reverse the obviousness type double patenting rejection of claims 44, 47, 48, 51-54 and 56-58 over Petite '740 and Chang (1995).

I. Obviousness type Double Patenting rejection over Petite '479, Petite '510 and Chang (1995)

The Examiner again argues that the "process of isolating PGCs from an embryo after stage 14 does not structurally or functionally distinguish the PGCs claimed from the PGCs inherently contained in the dissociated whole stage X embryo described by Petite." (Ans. 54).

Appellants contend "that one of ordinary skill in the art would find no motivation in the combination of either the '479 Patent or the '510 Patent with Chang (1995) to produce sustained cultures of undifferentiated cells from PGCs isolated from later than stage 14 chicken embryos (App. Br. 43). Appellants further argue "that it is known to those of skill in the art that ES cells cannot be 'isolated' from any stage of any embryo. Rather, they are produced by culturing certain cell types in vitro" (App. Br. 43).

In view of these conflicting positions, we frame the issue before us as follows:

Do claims 44, 47, 48, 51-57 define something that is an obvious variant of what is claimed in claims 1 of Petite ‘479 or Petite ‘510 further in view of Chang (1995)?

We incorporate the facts found for Chang (1995) supra.

Discussion of Obviousness Double Patenting rejection over Petite ‘479, Petite ‘510, and Chang (1995)

The Petite ‘479 and Petite ‘510 claims are generic, drawn to the genus of a “sustained avian cell culture consisting essentially of undifferentiated avian cells expressing an embryonic stem cell phenotype” (Petite ‘479, claim 1). The instant claims represent a species of these generic claims, in which the cells must comprise a mixture of primordial germ cells and stromal cells, and where the cells must be isolated from the embryonic genital ridge or gonad at a stage later than stage 14 of the Hamburger and Hamilton staging system (*see* App. Br. 46, claim 44).

In order to determine whether the instant species claims represent an obvious variant of the generic disclosures of claim 1 of Petite ‘479 or Petite ‘510, we need to address several specific considerations. The size of a genus in Petite ‘479 and ‘510 relative to a claimed subgenus in the instant claims is a central issue. Because the Petite ‘479 and Petite ‘510 patents claim a very broad genus of avian embryonic stem cells, this weighs against a determination that the relatively narrow subgenus in the instant claims of a specific mixture of primordial germ cells and stromal cells which must be drawn from particular stages in embryonic development and which must be isolated from the embryonic genital ridge or gonad is obvious over the

genus. *See, e.g., In re Baird*, 16 F.3d 380, 383 (Fed. Cir 1994) (“A disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds”). In this context, the Petite ‘479 and Petite ‘510 patent disclosures also indicate a preference for cells derived from stage X embryos, which leads away from the subgenus of the instant claims which are drawn to embryos at stages later than stage 14 (*see* FF 43, 44; claim 44).

Another related consideration is whether the prior art highlights any “typical,” “preferred,” or “optimum” species within the genus. Highlighted species different from those claimed may weigh against a determination of obviousness. *In re Baird*, 16 F.3d at 382. On the other hand, typical, preferred, or optimum species structurally similar to those claimed may be evidence supporting a determination of obviousness. *In re Dillon*, 919 F.2d 688, 696 (Fed. Cir. 1990). We recognize that Chang (1995) teaches a sustained culture of cells in which the chicken primordial germ cells from the embryonic genital ridge were isolated from an embryo at a stage later than stage 14 and which were cultured in conditioned media on a preconditioned feeder matrix including chicken stromal cells (FF 28-31). However, because Chang (1995) does not teach embryonic stem cell cultures, and only inherently comprises a sustained culture of embryonic stem cells, Chang (1995) does not highlight the specific cell types, cell sources or cell stages as optimal or preferred and does not support an obviousness double patenting rejection.

We are not persuaded by the Examiner's reasoning that the "process of isolating PGCs from an embryo after stage 14 does not structurally or functionally distinguish the PGCs claimed from the PGCs inherently contained in the dissociated whole stage X embryo described by Petite" (Ans. 54). While it is certainly possible that some of the cells from a stage X embryo will develop in vitro into the same type of cells as those derived from the genital ridge or gonads of a stage 14 embryo, the Examiner has not presented evidence or persuasive argument that this is probable or even likely (*see* FF 43-45).

We therefore reverse the obviousness type double patenting rejection of claims 44, 47, 48, 51-54 and 56-57 over Petite '479 and Petite '510 and Chang (1995).

CONCLUSION

In summary, the rejection of the claims 53-54 under 35 U.S.C. § 112, first paragraph for new matter is reversed. The rejection under 35 U.S.C. § 112, first paragraph for lack of enablement is affirmed with respect to claims 53 and 54 but reversed with respect to claims 44, 47, 48, 51, 52, and 56-58. The anticipation rejection over Chang (1995) for claims 44, 47, 48, 52, and 56 is affirmed. The anticipation rejection over Chang (1995) for claims 53, 54, and 58 is reversed. The anticipation rejection over Chang (1997) for claims 44, 47, 48, 52, and 56 is affirmed. The anticipation rejection over Chang (1997) for claims 53, 54 and 58 is reversed. The anticipation rejection over the Petite '740, Petite '479 and Petite '510 patents for claims 44, 47, 48, 51-54, and 56-58 is reversed. The obviousness rejection over Chang (1995) and Ponce de Leon '569 for claims 44, 47, 48,

52, and 58 is affirmed. The obviousness rejection over Chang (1995) and Ponce de Leon ‘569 for claims 53 and 54 is reversed. The obviousness type double patenting rejection of claims 44, 47, 48, 51-54 and 56-58 over Pettit ‘740 and Chang (1995) is reversed. The obviousness type double patenting rejection of claims 44, 47, 48, 51-54 and 56-57 over Pettit ‘479 and Pettit ‘510 and Chang (1995) is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED-IN-PART

lp

FREDMAN, *Administrative Patent Judge*, concurring.

While I concur with the majority's analysis on issues A and C-I and concur in the result, I respectfully dissent from the majority's conclusion in issue B that only claims 53 and 54 fail to meet the enablement requirement of 35 U.S.C. § 112, first paragraph. I would affirm the rejection of independent claim 44 and dependent claims 47, 48, 51, 52, and 56-58 as also lacking enablement under 35 U.S.C. § 112, first paragraph.

As the Examiner notes "[t]he generic lists of possible parameters described in the specification taken with the mere suggestion of maintaining 'embryo cells of the present invention . . . for at least one or two months' is not a reasonable amount of guidance because the number of combinations contemplated is vast" (Ans. 10). Claim 44, the independent claim, encompasses the vast number of combinations of sustained cultures, including cultures maintained in an undifferentiated state for one or two months (claims 53 and 54), as well as the additional period after the five days of culture shown in example 4 of the Specification (Spec. 21-22) until the one month period of claim 53.

The Federal Circuit has emphasized that broad claims must enable the complete scope of the claim, noting that "the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification" *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993).

The measure of whether the scope of protection is properly correlated is "if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 1577

(Fed. Cir. 1984). I think that the evidence presented by the Examiner (see FF 10-27) support the conclusion that claim 44 encompasses a large number of inoperative combinations, potentially beginning with any sustained culture of undifferentiated chicken cells that extends in duration longer than the 5 days exemplified and encompassing any length of time including one to two months to several years.

Recent Federal Circuit precedent has shown that claims which are broad enough to encompass significant nonenabled subject matter will be found nonenabled. *See Sitrick v. Dreamworks, LLC*, ___ F.3d ___, 2008 WL 269443 (“Because the asserted claims are broad enough to cover both movies and video games, the patents must enable both embodiments”). In accord is *Automotive Technologies Intern., Inc. v. BMW of North America, Inc.*, 501 F.3d 1274, 1285 (Fed. Cir. 2007)(“Disclosure of only mechanical side impact sensors does not permit one skilled in the art to make and use the invention as broadly as it was claimed, which includes electronic side impact sensors”). In my view, claim 44 is similar to the claims struck down by the Federal Circuit in *Sitrick* and *Automotive Technologies*, in which a broad claim expressly encompassed nonenabled embodiments which rendered the broad claim nonenabled.

I think that the Majority’s reliance on *In re Cortright*, 165 F.3d 1353, 1358-59 (Fed. Cir. 1999) is misplaced. *Cortright* relied upon a claim interpretation in which the court concluded that

one of ordinary skill would not construe “restoring hair growth” to mean ‘returning the user’s hair to its original state,’ as the board required. To the contrary, consistent with Cortright’s disclosure and that of other references, one of ordinary skill would construe this phrase as meaning that the

claimed method increases the amount of hair grown on the scalp but does not necessarily produce a full head of hair.

Cortright, 165 F.3d. 1359. Unlike in *Cortright*, one of ordinary skill in the art would read claim 44 in concert with claims 53 and 54 and would necessarily construe claim 44 consistent with Appellant's disclosure to encompass a sustained culture of one to two months, claims which the Majority agrees are nonenabled.

“[A]s part of the *quid pro quo* of the patent bargain, the applicant's specification must enable one of ordinary skill in the art to practice the full scope of the claimed invention.” *AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). I think that the Appellant has not satisfied the *quid pro quo* of the patent bargain for the full scope of claim 44 and accordingly, I would affirm the Examiner's rejection of claim 44 and dependent claims 47, 48, 51-54, and 56-58 as lacking enablement under 35 U.S.C. § 112, first paragraph.

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